CLINICAL VIGNETTE

Emerging Role of Lipoprotein(a) in the Diagnosis and Treatment of Coronary Artery Disease

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Case Report

Lipoprotein(a) [Lp(a)] testing is gaining recognition for clinical value in cardiovascular (CV) risk assessment. Research continues to highlight its strong link to atherosclerotic diseases such as coronary artery disease and stroke. Despite growing awareness, challenges remain in effectively treating elevated Lp(a) levels, as they are primarily genetically determined and less responsive to traditional lipid-lowering therapies. Addressing these challenges is important for the development of targeted treatments to reduce CV risk in affected individuals. The following clinical case illustrates some of the difficulties in the treatment of patients with elevated CV risk.

A 61-year-old woman presented to Cardiology to establish care. She had been clinically stable, adhering to a Mediterranean style diet, and performing regular, dedicated cardiovascular exercise at moderate to high level of intensity. The patient's brother was diagnosed with severe coronary artery disease at 65 years old. For this reason, she sought cardiovascular risk assessment. The patient's primary care physician obtained a fasting lipid panel and a computed tomographic (CT) coronary calcium scan. The patient's LDL cholesterol was 176 mg/dL (N<100mg/dL) and her coronary artery calcium score was 234, placing her in the 95th percentile rank for age group and gender. Lp(a) was also checked and was elevated at 178 nmol/L (N<75 nmol/L). She was initially started on atorvastatin however, several months later she reported severe muscle pain and weakness which significantly reduced her exercise tolerance. She was subsequently tried on rosuvastatin and pravastatin, but experienced similar side effects. Due to these problems, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, evolocumab, was started. Although the patient found the new regimen tolerable, it was concerning that LDL was not reduced to target levels and Lp(a) remained essentially unchanged (at 173 nmol/L).

Discussion

The history of Lp(a) testing, rooted in late 20th-century discoveries, has advanced in laboratory methods and understanding of clinical relevance. Initial studies, such as those by Berg et al. in 1986, identified Lp(a)'s association with atherosclerosis, paving the way for further research into its role in cardiovascular disease.[1] Subsequent refinements in measurement techniques, including the introduction of enzyme-linked immunosorbent assays (ELISA) and genetic testing, have enhanced accuracy and deepened insights into Lp(a)'s biology.[2,3]

Lipoprotein(a) is a low-density lipoprotein (LDL)-like particle with an apolipoprotein B-100 molecule covalently bound to apolipoprotein (a).[4] Circulating Lp(a) levels are primarily genetically determined,[5] and epidemiologic, genome-wide association, and mendelian randomization studies provide robust evidence that elevated Lp(a) levels are causally associated with atherosclerotic cardiovascular disease (ASCVD) risk.[5] Coronary artery calcium (CAC) is a highly specific marker of coronary atherosclerosis that is quantified using the Agatston method to yield the CAC score.[6] A CAC score captures the burden of subclinical coronary atherosclerosis and is a guideline-endorsed, independent predictor of ASCVD risk.[7,8] Mehta et al recently reported several important findings of independent and joint associations of Lp(a) and CAC score with ASCVD risk among participants of two multi-ethnic American epidemiologic cohorts free of clinical cardiovascular disease at baseline.[9] First, elevated Lp(a) level and CAC score were independently associated with incident ASCVD, after adjusting for traditional risk factors and each other. Second, participants with both elevated Lp(a) and CAC score were at significantly higher ACVD risk compared with those having neither risk marker elevated. Third, elevated Lp(a) level was associated with higher ASCVD risk among individuals with CAC score ≥100, whereas among individuals with CAC <100, ASCVD risk was similar with elevated or non-elevated Lp(a) level. Fourth, individuals with CAC score of zero were at low 10-year ASCVD risk even in the setting of an elevated Lp(a) level.

In response to the emerging role of Lp(a) as a cardiovascular risk marker, tailored therapeutic strategies have been explored to mitigate elevated Lp(a) levels. Pharmacological interventions, including niacin and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have shown promise in lowering Lp(a) concentrations, albeit with varying efficacy.[10] Novel therapeutic modalities such as antisense oligonucleotide therapies targeting apolipoprotein(a) synthesis represent a promising frontier in Lp(a)-specific management, offering potential avenues for precision medicine in CVD prevention.[11] However, challenges such as treatment adherence and long-term safety profiles warrant further investigation.

Incorporating Lp(a) testing into cardiovascular risk assessment shows potential for improving risk stratification and informing targeted interventions. Ongoing research is crucial to better understand the mechanisms by which Lp(a) contributes to cardiovascular risk and to refine its use in clinical settings. Additionally, thorough evaluation of new therapies aimed at lowering Lp(a) is essential to confirm their effectiveness, safety, and long-term benefits for cardiovascular health.

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